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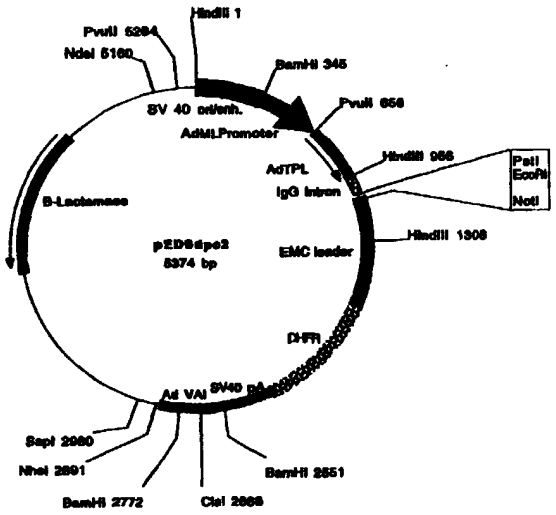
(57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This is a continuation-in-part of Ser. No. 60/XXX,XXX, filed December 13, 1996 (converted to provisional application from non-provisional application Ser. No. 08/766,263), which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 22 to nucleotide 462;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ1_1 deposited under accession number ATCC 98278;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ1_1 deposited under accession number ATCC 98278;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ1_1 deposited under accession number ATCC 98278;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ1_1 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 22 to nucleotide 462; the nucleotide sequence of the full-length protein coding sequence of clone AJ1_1 deposited under accession number ATCC 98278; or the nucleotide sequence of the mature protein coding sequence of clone AJ1_1 deposited under accession number ATCC 98278. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AJ1_1 deposited under accession number ATCC 98278. In yet other preferred

embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 from amino acid 52 to amino acid 147.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1 or SEQ ID NO:3.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 52 to amino acid 147;

(c) fragments of the amino acid sequence of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone AJ1_1 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2 from amino acid 52 to amino acid 147.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:4;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:4 from nucleotide 7 to nucleotide 1647;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:4 from nucleotide 1 to nucleotide 305;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AQ73_3 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AQ73_3 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AQ73_3 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AQ73_3 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:5;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:5 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:4 from nucleotide 7 to nucleotide 1647; the nucleotide sequence of SEQ ID NO:4 from nucleotide 1 to nucleotide 305; the nucleotide sequence of the full-length protein coding sequence of clone AQ73_3 deposited under accession number ATCC 98278; or the nucleotide sequence of the mature protein coding sequence of clone AQ73_3 deposited under accession number ATCC 98278. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AQ73_3 deposited under accession number ATCC 98278. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:5 from amino acid 1 to amino acid 68.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:4.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:5;

(b) the amino acid sequence of SEQ ID NO:5 from amino acid 1 to amino acid 68;

(c) fragments of the amino acid sequence of SEQ ID NO:5; and

(d) the amino acid sequence encoded by the cDNA insert of clone AQ73_3 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:5 or the amino acid sequence of SEQ ID NO:5 from amino acid 1 to amino acid 68.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6 from nucleotide 62 to nucleotide 757;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6 from nucleotide 357 to nucleotide 703;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BG142_1 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BG142_1 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG142_1 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG142_1 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:7;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:7 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:6 from nucleotide 62 to nucleotide 757; the nucleotide sequence of SEQ ID NO:6 from nucleotide 357 to nucleotide 703; the nucleotide sequence of the full-length protein coding

sequence of clone BG142_1 deposited under accession number ATCC 98278; or the nucleotide sequence of the mature protein coding sequence of clone BG142_1 deposited under accession number ATCC 98278. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BG142_1 deposited under accession number ATCC 98278. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:7 from amino acid 184 to amino acid 214.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:6.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:7;

(b) the amino acid sequence of SEQ ID NO:7 from amino acid 184 to amino acid 214;

(c) fragments of the amino acid sequence of SEQ ID NO:7; and

(d) the amino acid sequence encoded by the cDNA insert of clone BG142_1 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:7 or the amino acid sequence of SEQ ID NO:7 from amino acid 184 to amino acid 214.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8 from nucleotide 404 to nucleotide 535;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8 from nucleotide 1 to nucleotide 666;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BV66_1 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BV66_1 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BV66_1 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BV66_1 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:9;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:9 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:8 from nucleotide 404 to nucleotide 535; the nucleotide sequence of SEQ ID NO:8 from nucleotide 1 to nucleotide 666; the nucleotide sequence of the full-length protein coding sequence of clone BV66_1 deposited under accession number ATCC 98278; or the nucleotide sequence of the mature protein coding sequence of clone BV66_1 deposited under accession number ATCC 98278. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BV66_1 deposited under accession number ATCC 98278. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:9 from amino acid 1 to amino acid 38.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:8.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:9;

(b) the amino acid sequence of SEQ ID NO:9 from amino acid 1 to amino acid 38;

(c) fragments of the amino acid sequence of SEQ ID NO:9; and

(d) the amino acid sequence encoded by the cDNA insert of clone BV66_1 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:9 or the amino acid sequence of SEQ ID NO:9 from amino acid 1 to amino acid 38.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:10;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:10 from nucleotide 1204 to nucleotide 1389;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:10 from nucleotide 881 to nucleotide 1380;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BV291_3 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BV291_3 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BV291_3 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BV291_3 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:11;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:11 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:10 from nucleotide 1204 to nucleotide 1389; the nucleotide sequence of SEQ ID NO:10 from nucleotide 881 to nucleotide 1380; the nucleotide sequence of the full-length protein coding sequence of clone BV291_3 deposited under accession number ATCC 98278; or the nucleotide sequence of the mature protein coding sequence of clone BV291_3 deposited under accession number ATCC 98278. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BV291_3 deposited under accession number ATCC 98278. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:11 from amino acid 1 to amino acid 59.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:10.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:11;

(b) the amino acid sequence of SEQ ID NO:11 from amino acid 1 to amino acid 59;

(c) fragments of the amino acid sequence of SEQ ID NO:11; and

(d) the amino acid sequence encoded by the cDNA insert of clone BV291_3 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:11 or the amino acid sequence of SEQ ID NO:11 from amino acid 1 to amino acid 59.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 189 to nucleotide 1115;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 1 to nucleotide 451;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CK201_1 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CK201_1 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CK201_1 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CK201_1 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:13 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:12 from nucleotide 189 to nucleotide 1115; the nucleotide sequence of SEQ ID NO:12 from nucleotide 1 to nucleotide 451; the nucleotide sequence of the full-length protein coding sequence of clone CK201_1 deposited under accession number ATCC 98278; or the nucleotide sequence of the mature protein coding sequence of clone CK201_1 deposited under accession number ATCC 98278. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CK201_1 deposited under accession number ATCC 98278. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13 from amino acid 1 to amino acid 88.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:12.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:13;

(b) the amino acid sequence of SEQ ID NO:13 from amino acid 1 to amino acid 88;

(c) fragments of the amino acid sequence of SEQ ID NO:13; and

(d) the amino acid sequence encoded by the cDNA insert of clone CK201_1 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:13 or the amino acid sequence of SEQ ID NO:13 from amino acid 1 to amino acid 88.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14 from nucleotide 117 to nucleotide 923;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14 from nucleotide 174 to nucleotide 923;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14 from nucleotide 1 to nucleotide 316;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CQ331_2 deposited under accession number ATCC 98278;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CQ331_2 deposited under accession number ATCC 98278;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CQ331_2 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CQ331_2 deposited under accession number ATCC 98278;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:15;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:15 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:14 from nucleotide 117 to nucleotide 923; the nucleotide sequence of SEQ ID NO:14 from nucleotide 174 to nucleotide 923; the nucleotide sequence of SEQ ID NO:14 from nucleotide 1 to nucleotide 316; the nucleotide sequence of the full-length protein coding sequence of clone CQ331_2 deposited under accession number ATCC 98278; or the nucleotide sequence of the mature protein coding sequence of clone CQ331_2 deposited under accession number ATCC 98278. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CQ331_2 deposited under accession number ATCC 98278. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:15 from amino acid 1 to amino acid 57.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:14.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:15;

(b) the amino acid sequence of SEQ ID NO:15 from amino acid 1 to amino acid 57;

(c) fragments of the amino acid sequence of SEQ ID NO:15; and

(d) the amino acid sequence encoded by the cDNA insert of clone CQ331_2 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:15 or the amino acid sequence of SEQ ID NO:15 from amino acid 1 to amino acid 57.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16 from nucleotide 223 to nucleotide 483;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16 from nucleotide 22 to nucleotide 397;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CT550_1 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CT550_1 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CT550_1 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CT550_1 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:17;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:17 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:16 from nucleotide 223 to nucleotide 483; the nucleotide sequence of SEQ ID NO:16 from nucleotide 22 to nucleotide 397; the nucleotide sequence of the full-length protein

coding sequence of clone CT550_1 deposited under accession number ATCC 98278; or the nucleotide sequence of the mature protein coding sequence of clone CT550_1 deposited under accession number ATCC 98278. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CT550_1 deposited under accession number ATCC 98278. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:17 from amino acid 1 to amino acid 58.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:16.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:17;

(b) the amino acid sequence of SEQ ID NO:17 from amino acid 1 to amino acid 58;

(c) fragments of the amino acid sequence of SEQ ID NO:17; and

(d) the amino acid sequence encoded by the cDNA insert of clone CT550_1 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:17 or the amino acid sequence of SEQ ID NO:17 from amino acid 1 to amino acid 58.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 112 to nucleotide 969;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 154 to nucleotide 969;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 1 to nucleotide 423;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CT585_1 deposited under accession number ATCC 98278;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CT585_1 deposited under accession number ATCC 98278;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CT585_1 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CT585_1 deposited under accession number ATCC 98278;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:19;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:18 from nucleotide 112 to nucleotide 969; the nucleotide sequence of SEQ ID NO:18 from nucleotide 154 to nucleotide 969; the nucleotide sequence of SEQ ID NO:18 from nucleotide 1 to nucleotide 423; the nucleotide sequence of the full-length protein coding sequence of clone CT585_1 deposited under accession number ATCC 98278; or the nucleotide sequence of the mature protein coding sequence of clone CT585_1 deposited under accession number ATCC 98278. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CT585_1 deposited under accession number ATCC 98278. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:19 from amino acid 1 to amino acid 104.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:18.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:19;

(b) the amino acid sequence of SEQ ID NO:19 from amino acid 1 to amino acid 104;

(c) fragments of the amino acid sequence of SEQ ID NO:19; and

(d) the amino acid sequence encoded by the cDNA insert of clone CT585_1 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:19 or the amino acid sequence of SEQ ID NO:19 from amino acid 1 to amino acid 104.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20 from nucleotide 37 to nucleotide 2766;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20 from nucleotide 243 to nucleotide 789;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CT797_3 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CT797_3 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CT797_3 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CT797_3 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:21;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:21 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:20 from nucleotide 37 to nucleotide 2766; the nucleotide sequence of SEQ ID NO:20 from nucleotide 243 to nucleotide 789; the nucleotide sequence of the full-length protein coding sequence of clone CT797_3 deposited under accession number ATCC 98278; or the nucleotide sequence of the mature protein coding sequence of clone CT797_3 deposited under accession number ATCC 98278. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CT797_3 deposited under accession number ATCC 98278. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:21 from amino acid 75 to amino acid 251.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:20.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:21;

(b) the amino acid sequence of SEQ ID NO:21 from amino acid 75 to amino acid 251;

(c) fragments of the amino acid sequence of SEQ ID NO:21; and

(d) the amino acid sequence encoded by the cDNA insert of clone CT797_3 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:21 or the amino acid sequence of SEQ ID NO:21 from amino acid 75 to amino acid 251.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions.

Processes are also provided for producing a protein, which comprise:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

(b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation

proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Clone "AJ1_1"

A polynucleotide of the present invention has been identified as clone "AJ1_1". AJ1_1 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AJ1_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AJ1_1 protein").

The nucleotide sequence of the 5' portion of AJ1_1 as presently determined is reported in SEQ ID NO:1. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:2. The predicted amino acid sequence of the AJ1_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2. Additional nucleotide sequence from the 3' portion of AJ1_1, including the polyA tail, is reported in SEQ ID NO:3.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AJ1_1 should be approximately 925 bp.

The predicted amino acid sequence disclosed herein for AJ1_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AJ1_1 protein demonstrated at least some similarity to sequences identified as U39060 (GRIP1 [Mus musculus]). Based upon sequence similarity, AJ1_1 proteins and each similar protein or peptide may share at least some activity.

Clone "AQ73_3"

A polynucleotide of the present invention has been identified as clone "AQ73_3". AQ73_3 was isolated from a human adult ovary (PA-1 teratocarcinoma, untreated tissue pooled with retinoic-acid-treated and activin-treated tissue) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AQ73_3 is a full-length clone,

including the entire coding sequence of a secreted protein (also referred to herein as "AQ73_3 protein").

The nucleotide sequence of AQ73_3 as presently determined is reported in SEQ ID NO:4. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AQ73_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:5.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AQ73_3 should be approximately 2800 bp.

The nucleotide sequence disclosed herein for AQ73_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AQ73_3 demonstrated at least some similarity with sequences identified as AA514474 (nf57g01.s1 NCI_CGAP_Co3 Homo sapiens cDNA clone 924048), T47520 (Human hepatoma-derived growth factor (HDGF-2) cDNA), W24708 (zb62e08.r1 Soares fetal lung NbHL19W Homo sapiens cDNA clone 308198 5'), and W45513 (zc27g08.s1 Soares senescent fibroblasts NbHSF Homo sapiens cDNA clone 323582 3'). The predicted amino acid sequence disclosed herein for AQ73_3 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AQ73_3 protein demonstrated at least some similarity to sequences identified as D16431 (hepatoma-derived GF [Homo sapiens]), D63707 (mouse hepatoma derived growth factor (HDGF) [Mus musculus]), R66727 (Human hepatoma derived growth factor), U18997 (ORF_f299 [Escherichia coli]), U97193 (similar to S. cerevisiae SIR2 (SP P06700) and mouse hepatoma derived growth factor HDGF (NID g945418) [Caenorhabditis elegans]), and W09404 (Human hepatoma-derived growth factor (HDGF-2)). Based upon sequence similarity, AQ73_3 proteins and each similar protein or peptide may share at least some activity.

Clone "BG142_1"

A polynucleotide of the present invention has been identified as clone "BG142_1". BG142_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BG142_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BG142_1 protein").

The nucleotide sequence of BG142_1 as presently determined is reported in SEQ ID NO:6. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BG142_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:7.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BG142_1 should be approximately 1100 bp.

The nucleotide sequence disclosed herein for BG142_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BG142_1 demonstrated at least some similarity with sequences identified as AA170261 (ms87h11.r1 Soares mouse 3NbMS Mus musculus cDNA clone 618597 5' similar to TR E245601 E245601 G-RICH BOX-BINDING PROTEIN), L04282 (Human CACCC box-binding protein mRNA, complete cds), N27696 (yx51h12.r1 Homo sapiens cDNA clone 265319 5'), W96110 (ze09a11.r1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 358460 5'), and W96111 (ze09a11.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 358460 3'). The predicted amino acid sequence disclosed herein for BG142_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted BG142_1 protein demonstrated at least some similarity to sequences identified as U80078 (transcription factor BFCOL1 [Mus musculus]) and X98096 (G-rich box-binding protein [Mus musculus]). Based upon sequence similarity, BG142_1 proteins and each similar protein or peptide may share at least some activity.

Clone "BV66_1"

A polynucleotide of the present invention has been identified as clone "BV66_1". BV66_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BV66_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BV66_1 protein").

The nucleotide sequence of BV66_1 as presently determined is reported in SEQ ID NO:8. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BV66_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:9.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BV66_1 should be approximately 870 bp.

The nucleotide sequence disclosed herein for BV66_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. No hits were found in the database. The nucleotide sequence of BV66_1 indicates that it may contain a TAAA1 simple repeat element.

Clone "BV291_3"

A polynucleotide of the present invention has been identified as clone "BV291_3". BV291_3 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BV291_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BV291_3 protein").

The nucleotide sequence of BV291_3 as presently determined is reported in SEQ ID NO:10. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BV291_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:11.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BV291_3 should be approximately 2000 bp.

The nucleotide sequence disclosed herein for BV291_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BV291_3 demonstrated at least some similarity with sequences identified as H10954 (ym06e09.r1 Homo sapiens cDNA clone 47034 5'), H10955 (ym06e09.s1 Homo sapiens cDNA clone 47034 3'), N25300 (yw52c10.s1 Homo sapiens cDNA clone 255858 3'), T25940 (Human gene signature HUMGS08173), T68890 (yc30g11.s1 Homo sapiens cDNA clone 82244 3'), T78286 (yc99a08.r1 Homo sapiens cDNA clone 24033 5'), Z39987 (H. sapiens partial cDNA sequence; clone c-1oh05), and Z47073 (Caenorhabditis elegans cosmid ZC506). The predicted amino acid sequence disclosed herein for BV291_3 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted BV291_3 protein demonstrated at least some similarity to sequences identified as X02155 (BTTGR_1 thyroglobulin [Bos taurus]). Based upon sequence similarity, BV291_3 proteins and each

similar protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the BV291_3 protein sequence centered around amino acid 48 of SEQ ID NO:11.

Clone "CK201_1"

A polynucleotide of the present invention has been identified as clone "CK201_1". CK201_1 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CK201_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CK201_1 protein").

The nucleotide sequence of CK201_1 as presently determined is reported in SEQ ID NO:12. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CK201_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:13.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CK201_1 should be approximately 1080 bp.

The nucleotide sequence disclosed herein for CK201_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CK201_1 demonstrated at least some similarity with sequences identified as AA129133 (zo09h12.s1 Stratagene neuroepithelium NT2RAMI 937234 Homo sapiens cDNA clone 567239 3' similar to contains Alu repetitive element), D81444 (Human fetal brain cDNA 5'-end GEN-164G10), R36326 (yg69h09.r1 Homo sapiens cDNA clone 38821 5'), T08553 (Oncogene R-ras mutant cDNA (exons 2-6)), T31595 (Probe (BLUR13) for Alu repeat sequence), X03273 (Human Alu-family cluster 5' of alpha(1)-acid glycoprotein gene), and X69907 (H.sapiens gene for mitochondrial ATP synthase c subunit). The predicted amino acid sequence disclosed herein for CK201_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted CK201_1 protein demonstrated at least some similarity to sequences identified as D21827 (major surface glycoprotein [Pneumocystis carinii]). Based upon sequence similarity, CK201_1 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of CK201_1 indicates that it may contain an Alu repetitive element.

Clone "CQ331_2"

A polynucleotide of the present invention has been identified as clone "CQ331_2". CQ331_2 was isolated from a human adult heart cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CQ331_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CQ331_2 protein").

The nucleotide sequence of CQ331_2 as presently determined is reported in SEQ ID NO:14. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CQ331_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:15. Amino acids 7 to 19 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 20, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CQ331_2 should be approximately 1600 bp.

The nucleotide sequence disclosed herein for CQ331_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CQ331_2 demonstrated at least some similarity with sequences identified as J03766 (Canine cardiac calsequestrin mRNA, complete cds), L29766 (Homo sapiens epoxide hydrolase (EPHX) gene, complete cds), N83601 (KK1173F Homo sapiens cDNA clone KK1173 5' similar to CALSEQUESTRIN (CARDIAC)), T99646 (ye73f12.s1 Homo sapiens cDNA clone 123407 3' similar to contains Alu repetitive element;contains PTR5 repetitive element), and W76326 (zd60d04.r1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 345031 5' similar to contains Alu repetitive element). The predicted amino acid sequence disclosed herein for CQ331_2 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted CQ331_2 protein demonstrated at least some similarity to sequences identified as J03766 (DOGCAL_1 Canine cardiac calsequestrin mRNA, complete cds [Canis canis]) and X55040 (calsequestrin [Oryctolagus cuniculus]). Based upon sequence similarity, CQ331_2 proteins and each similar protein or peptide may share at least some activity.

Clone "CT550_1"

A polynucleotide of the present invention has been identified as clone "CT550_1". CT550_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CT550_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CT550_1 protein").

The nucleotide sequence of CT550_1 as presently determined is reported in SEQ ID NO:16. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CT550_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:17.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CT550_1 should be approximately 1070 bp.

The nucleotide sequence disclosed herein for CT550_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. No hits were found in the database. The TopPredII computer program predicts a potential transmembrane domain within the CT550_1 protein sequence centered around amino acid 25 of SEQ ID NO:17.

Clone "CT585_1"

A polynucleotide of the present invention has been identified as clone "CT585_1". CT585_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CT585_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CT585_1 protein").

The nucleotide sequence of CT585_1 as presently determined is reported in SEQ ID NO:18. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CT585_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:19. Amino acids 2 to 14 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 15, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CT585_1 should be approximately 2710 bp.

The nucleotide sequence disclosed herein for CT585_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CT585_1 demonstrated at least some similarity with sequences identified as AA069442 (zf74b02.s1 Soares pineal gland N3HPG Homo sapiens cDNA clone 382635 3'), L38961 (Homo sapiens putative transmembrane protein (B5) mRNA, complete cds), N34932 (yy49b10.s1 Homo sapiens cDNA clone 276859 3'), N60101 (TgESTzy11f10.r1 Toxoplasma gondii cDNA clone tgzy11f10.r1 5'), and U13019 (Caenorhabditis elegans cosmid T12A2). The predicted amino acid sequence disclosed herein for CT585_1 was searched against the GenPept, GeneSeq, and SwissProt amino acid sequence databases using the BLASTX search protocol. The predicted CT585_1 protein demonstrated at least some similarity to sequences identified as L34260 (transmembrane protein [Mus musculus]), L38961 (transmembrane protein [Homo sapiens]), P46975 (Caenorhabditis elegans oligosaccharyl transferase stt3 [Caenorhabditis elegans]), and U13019 (Caenorhabditis elegans cosmid T12A2 [Caenorhabditis elegans]). Based upon sequence similarity, CT585_1 proteins and each similar protein or peptide may share at least some activity.

Clone "CT797_3"

A polynucleotide of the present invention has been identified as clone "CT797_3". CT797_3 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CT797_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CT797_3 protein").

The nucleotide sequence of CT797_3 as presently determined is reported in SEQ ID NO:20. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CT797_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:21.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CT797_3 should be approximately 3300 bp.

The nucleotide sequence disclosed herein for CT797_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CT797_3 demonstrated at least some similarity with sequences identified as AA573847 (nk08d06.s1 NCI_CGAP_Co2 Homo sapiens cDNA clone IMAGE:1012907). The predicted amino acid sequence disclosed herein for CT797_3 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted CT797_3 protein demonstrated at least some similarity to sequences identified as U18309 (chromokinesin [Gallus gallus]) and Z82271 (T01G1.1 [Caenorhabditis elegans]). Based upon sequence similarity, CT797_3 proteins and each similar protein or peptide may share at least some activity.

Deposit of Clones

Clones AJ1_1, AQ73_3, BG142_1, BV66_1, BV291_3, CK201_1, CQ331_2, CT550_1, CT585_1 and CT797_3 were deposited on December 13, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and were given the accession number ATCC 98278, from which each clone comprising a particular polynucleotide is obtainable. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b).

Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Fig. 1. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* **19**: 4485-4490); the pNOTs vector was derived from pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* **9**: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the ClaI site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

Clone	Probe Sequence
AJ1_1	SEQ ID NO:22
AQ73_3	SEQ ID NO:23
BG142_1	SEQ ID NO:24
BV66_1	SEQ ID NO:25
BV291_3	SEQ ID NO:26
CK201_1	SEQ ID NO:27
CQ331_2	SEQ ID NO:28
CT550_1	SEQ ID NO:29
CT585_1	SEQ ID NO:30, SEQ ID NO:32
CT797_3	SEQ ID NO:31

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoaramidite residue rather than a nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramadite) (Glen Research, cat. no. 10-1953)).

The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with g-^{32}P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated

label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S.

McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which the cDNA sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides .

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp)‡	Hybridization Temperature and Buffer†	Wash Temperature and Buffer†
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T_B*; 1xSSC	T_B*; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T_D*; 1xSSC	T_D*; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T_F*; 1xSSC	T_F*; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T_H*; 4xSSC	T_H*; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T_J*; 4xSSC	T_J*; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T_L*; 2xSSC	T_L*; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T_N*; 6xSSC	T_N*; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T_P*; 6xSSC	T_P*; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T_R*; 4xSSC	T_R*; 4xSSC

‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

†: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6($\log_{10}$[Na^+]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na^+] is the concentration of sodium ions in the hybridization buffer ([Na^+] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium*, or any bacterial

strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant

methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which

the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is

evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for

example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or

tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, *89*:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of

viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface.

Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter

7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent

myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland,

H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of

congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and

Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the

first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can used to generate antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used

to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic

lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein

and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines

or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium

Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1ng to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where

abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect

the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Jacobs, Kenneth
McCoy, John M.
LaVallie, Edward R.
Racie, Lisa A.
Merberg, David
Treacy, Maurice
Spaulding, Vikki
Agostino, Michael J.

(ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(iii) NUMBER OF SEQUENCES: 32

(iv) CORRESPONDENCE ADDRESS:
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(C) CITY: Cambridge
(D) STATE: MA
(E) COUNTRY: U.S.A.
(F) ZIP: 02140

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Sprunger, Suzanne A.
(B) REGISTRATION NUMBER: 41,323

(ix) TELECOMMUNICATION INFORMATION:
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 462 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GTGGAAGGAG TGGATAATAA AATGAGTCAG TGCACCAGCT CCACCATTCC TAGCTCAAGT 60

CAAGAGAAAG ACCCTAAAAT TAAGACAGAG ACAAGTGAAG AGGGATCTGG AGACTTGGAT 120

AATCTAGATG CTATTCTTGG TGATCTGACT AGTTCTGACT TTTACAATAA TTCCATATCC 180

TCAAATGGTA GTCATCTGGG GACTAAGCAA CAGGTGTTTC AAGGAACTAA TTCTCTGGGT 240

TTGAAAAGTT CACAGTCTGT GCAGTCTATT CGTCCTCCAT ATAACCGAGC AGTGTCTCTG 300

GATAGCCCTG TTTCTGTTGG CTCAAGTCCT CCAGTAAAAA ATATCAGTGC TTTCCCCATG 360

TTACCAAAGC AACCCATGTT GGGTGGGAAT CCAAGAATGA TGGATAGTCA RGAAAATTAT 420

GGCTCAAGTA TGGGAGACTG GGGCTTACCA AACTCAAAGG CC 462

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 147 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Ser Gln Cys Thr Ser Ser Thr Ile Pro Ser Ser Ser Gln Glu Lys
1 5 10 15

Asp Pro Lys Ile Lys Thr Glu Thr Ser Glu Glu Gly Ser Gly Asp Leu
20 25 30

Asp Asn Leu Asp Ala Ile Leu Gly Asp Leu Thr Ser Ser Asp Phe Tyr
35 40 45

Asn Asn Ser Ile Ser Ser Asn Gly Ser His Leu Gly Thr Lys Gln Gln
50 55 60

Val Phe Gln Gly Thr Asn Ser Leu Gly Leu Lys Ser Ser Gln Ser Val
65 70 75 80

Gln Ser Ile Arg Pro Pro Tyr Asn Arg Ala Val Ser Leu Asp Ser Pro
85 90 95

Val Ser Val Gly Ser Ser Pro Pro Val Lys Asn Ile Ser Ala Phe Pro
100 105 110

Met Leu Pro Lys Gln Pro Met Leu Gly Gly Asn Pro Arg Met Met Asp
115 120 125

Ser Gln Glu Asn Tyr Gly Ser Ser Met Gly Asp Trp Gly Leu Pro Asn
130 135 140

Ser Lys Ala
145

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 119 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAA 60

AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAA 119

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3316 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GGTAAGATGG CGGCTGTGAG TCTGCGGCTC GGCGACTTGG TGTGGGGGAA ACTCGGCCGA 60

TATCCTCCTT GGCCAGGAAA GATTGTTAAT CCACCAAAGG ACTTGAAGAA ACCTCGCGGA 120

AAGAAATGCT TCTTTGTGAA ATTTTTTGGA ACAGAAGATC ATGCCTGGAT CAAAGTGGAA 180

CAGCTGAAGC CATATCATGC TCATAAAGAG GAAATGATAA AAATTAACAA GGGTAAACGA 240

TTCCAGCAAG CGGTAGATGC TGTCGAAGAG TTCCTCAGGA GAGCCAAAGG GAAAGACCAG 300

ACGTCATCCC ACAATTCTTC TGATGACAAG AATCGACGTA ATTCCAGTGA GGAGAGAAGT 360

AGGCCAAACT CAGGTGATGA GAAGCGCAAA CTTAGCCTGT CTGAAGGGAA GGTGAAGAAG 420

AACATGGGAG AAGGAAAGAA GAGGGTGTCT TCAGGCTCTT CAGAGAGAGG CTCCAAATCC 480

CCTCTGAAAA GAGCCCAAGA GCAAAGTCCC CGGAAGCGGG GTCGGCCCCC AAAGGATGAG 540

AAGGATCTCA CCATCCCGGA GTCTAGTACC GTGAAGGGGA TGATGGCCGG ACCGATGGCC 600

GCGTTTAAAT GGCAGCCAAC CGCAAGCGAG CCTGTTAAAG ATGCAGATCC TCATTTCCAT 660

CATTTCCTGC TAAGCCAAAC AGAGAAGCCA GCTGTCTGTT ACCAGGCAAT CACGAAGAAG 720

TTGAAAATAT GTGAAGAGGA AACTGGCTCC ACCTCCATCC AGGCAGCTGA CAGCACAGCC 780

GTGAATGGCA GCATCACACC CACAGACAAA AAGATAGGAT TTTTGGGCCT TGGTCTCATG 840

GGAAGTGGAA TCGTCTCCAA CTTGCTAAAA ATGGGTCACA CAGTGACTGT CTGGAACCGC 900

ACTGCAGAGA AAGAGGGGGC CCGTCTGGGA AGAACCCCCG CTGAAGTCGT CTCAACCTGC 960

GACATCACTT TCGCCTGCGT GTCGGATCCC AAGGCGGCCA AGGACCTGGT GCTGGGCCCC 1020

AGTGGTGTGC TGCAAGGGAT CCGCCCTGGG AAGTGCTACG TGGACATGTC AACAGTGGAC 1080

GCTGACACCG TCACTGAGCT GGCCCAGGTG ATTGTGTCCA GGGGGGGGCG CTTTCTGGAA 1140

GCCCCCGTCT CAGGGAATCA GCAGCTGTCT AATGACGGGA TGTTGGTGAT CTTAGCGGCT 1200

GGAGACAGGG GCTTATATGA GGACTGCAGC AGCTGCTTCC AGGCGATGGG GAAGACCTCC 1260

TTCTTCCTAG GTGAAGTGGG CAATGCAGCC AAGATGATGC TGATCGTGAA CATGGTCCAA 1320

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AAGGATCTCC GCTTAGCCAT TGCGCTGGGT GATGCGGTCA ACCATCCGAC TCCCATGGCA 1560

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TCCGCCGTGT ACCGAGCCTA CATACACTAA GCTGTCGACA CCCCGCCCTC ACCCCTCCAA 1680

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CAGCCCACCT ATCTCCATTT CCTTTTATAC AGACTTTGAG ACTTGCCATC AGCACAGCAC 1800

ACAGCAGCAC CCTTCCCCTG AGGCCGGTGG GGAGGGGACA AGTGTCAGCA GGATTGGCGT 1860

GTGGGAAAGC TCTTGAGCTG GGCACTGGCC CCCCGGACGA GGTGGCTGTG TGTTCACACA 1920

CACACACACA CACACACACA CACAGGCTCT CGCCCCAGGA TAGAAGCTGC CCAGAAACTG 1980

CTGCCTGGCT TTTTTTCTTC CGAGCTTGTC TTATCTCAAA CCCCTTCCAG TCAAGGAACT 2040

AGAATCAGCA ACGAGAGTTG GAAGCCTTCC CACAGCTTCC CCCAGAGCGA AGAGGCTGTA 2100

GTCATGTCCC CATCCCCCAC TGGATTCCCT ACAAGGAGAG GCCTTGGGCC CAGATGAGCC 2160

AGTACAGACT CCAGACAGAG GGGCCCTTGG GGCCCTCCAA CCTCAGGTGA TGAGCTGAGA 2220

AAGATGTTCA CGTCTAAGCG TCCAGTGTGC ACCCAGCGCT CCATAGACGC CTTTGTGAAC 2280

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ATACGGAAAC GAGTGTCTTC ACTCCAGCCA GCATCATGGT CTTCGGTGCT TCCCGGGCCC 2460

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GTAATTATAT ATAGGGTGGC CACACTAGGG CGGGGTCCTT CCCCCCTCAC AGCTTTGGCC 2760

CCTTTCAGAG ATTAGAAACT GGGTTAGAGG ATTGCAGAAG ACGAGTGGGG GGAGGGCAGG 2820

GAAGATGCCT GTCGGGTTTT TAGCACAGTT CATTTCACTG GGATTTTGAA GCATTTCTGT 2880

CTGGACACAA AGCCTGTTCT AGTCCTGGCG GAACACACTG GGGGTGGGGG CGGGGGAAGA 2940

TGCGGTAATG AAACCGGTTA GTCAATTTTG TCTTAATATT GTTGACAATT CTGTAAAGTT 3000

CCTTTTTATG AATATTTCTG TTTAAGCTAT TTCACCTTTC TTTTGAAATC CTTCCCTTTT 3060

AAGGAGAAAA TGTGACACTT GTGAAAAAGC TTGTAAGAAA GCCCCTCCCT TTTTTCTTTA 3120

AACCTTTAAA TGACAAATCT AGGTAATTAA GGTTGTGAAT TTTTATTTTT GCTTTGTTTT 3180

TAATGAACAT TTGTCTTTCA GAATAGGATT GTGTGATAAT GTTTAAATGG CAAAAACAAA 3240

ACATGATTTT GTGCAATTAA CAAAGCTACT GCAAGAAAAA TAAAACACTT CTTGGTAACA 3300

CAAAAAAAAA AAAAAA 3316

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 547 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
Met Ala Ala Val Ser Leu Arg Leu Gly Asp Leu Val Trp Gly Lys Leu
1               5                  10                  15

Gly Arg Tyr Pro Pro Trp Pro Gly Lys Ile Val Asn Pro Pro Lys Asp
            20                  25                  30

Leu Lys Lys Pro Arg Gly Lys Lys Cys Phe Phe Val Lys Phe Phe Gly
        35                  40                  45

Thr Glu Asp His Ala Trp Ile Lys Val Glu Gln Leu Lys Pro Tyr His
    50                  55                  60

Ala His Lys Glu Glu Met Ile Lys Ile Asn Lys Gly Lys Arg Phe Gln
65                  70                  75                  80

Gln Ala Val Asp Ala Val Glu Glu Phe Leu Arg Arg Ala Lys Gly Lys
                85                  90                  95

Asp Gln Thr Ser Ser His Asn Ser Ser Asp Asp Lys Asn Arg Arg Asn
            100                 105                 110

Ser Ser Glu Glu Arg Ser Arg Pro Asn Ser Gly Asp Glu Lys Arg Lys
        115                 120                 125

Leu Ser Leu Ser Glu Gly Lys Val Lys Lys Asn Met Gly Glu Gly Lys
    130                 135                 140

Lys Arg Val Ser Ser Gly Ser Ser Glu Arg Gly Ser Lys Ser Pro Leu
145                 150                 155                 160

Lys Arg Ala Gln Glu Gln Ser Pro Arg Lys Arg Gly Arg Pro Pro Lys
                165                 170                 175

Asp Glu Lys Asp Leu Thr Ile Pro Glu Ser Ser Thr Val Lys Gly Met
            180                 185                 190

Met Ala Gly Pro Met Ala Ala Phe Lys Trp Gln Pro Thr Ala Ser Glu
        195                 200                 205

Pro Val Lys Asp Ala Asp Pro His Phe His His Phe Leu Leu Ser Gln
    210                 215                 220

Thr Glu Lys Pro Ala Val Cys Tyr Gln Ala Ile Thr Lys Lys Leu Lys
225                 230                 235                 240

Ile Cys Glu Glu Glu Thr Gly Ser Thr Ser Ile Gln Ala Ala Asp Ser
                245                 250                 255

Thr Ala Val Asn Gly Ser Ile Thr Pro Thr Asp Lys Lys Ile Gly Phe
            260                 265                 270
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Leu Gly Leu Gly Leu Met Gly Ser Gly Ile Val Ser Asn Leu Leu Lys
        275                 280                 285

Met Gly His Thr Val Thr Val Trp Asn Arg Thr Ala Glu Lys Glu Gly
    290                 295                 300

Ala Arg Leu Gly Arg Thr Pro Ala Glu Val Val Ser Thr Cys Asp Ile
305                 310                 315                 320

Thr Phe Ala Cys Val Ser Asp Pro Lys Ala Ala Lys Asp Leu Val Leu
                325                 330                 335

Gly Pro Ser Gly Val Leu Gln Gly Ile Arg Pro Gly Lys Cys Tyr Val
            340                 345                 350

Asp Met Ser Thr Val Asp Ala Asp Thr Val Thr Glu Leu Ala Gln Val
        355                 360                 365

Ile Val Ser Arg Gly Gly Arg Phe Leu Glu Ala Pro Val Ser Gly Asn
    370                 375                 380

Gln Gln Leu Ser Asn Asp Gly Met Leu Val Ile Leu Ala Ala Gly Asp
385                 390                 395                 400

Arg Gly Leu Tyr Glu Asp Cys Ser Ser Cys Phe Gln Ala Met Gly Lys
                405                 410                 415

Thr Ser Phe Phe Leu Gly Glu Val Gly Asn Ala Ala Lys Met Met Leu
            420                 425                 430

Ile Val Asn Met Val Gln Gly Ser Phe Met Ala Thr Ile Ala Glu Gly
        435                 440                 445

Leu Thr Leu Ala Gln Val Thr Gly Gln Ser Gln Gln Thr Leu Leu Asp
    450                 455                 460

Ile Leu Asn Gln Gly Gln Leu Ala Ser Ile Phe Leu Asp Gln Lys Cys
465                 470                 475                 480

Gln Asn Ile Leu Gln Gly Asn Phe Lys Pro Asp Phe Tyr Leu Lys Tyr
                485                 490                 495

Ile Gln Lys Asp Leu Arg Leu Ala Ile Ala Leu Gly Asp Ala Val Asn
            500                 505                 510

His Pro Thr Pro Met Ala Ala Ala Ala Asn Glu Val Tyr Lys Arg Ala
        515                 520                 525

Lys Ala Leu Asp Gln Ser Asp Asn Asp Met Ser Ala Val Tyr Arg Ala
    530                 535                 540

Tyr Ile His
545
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1097 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

ATTGGTTCAA GAAGAAAATT TGAGCCCAGG CACCCAAACA CCTTCAAATG ATAAAGCAAG 60

TATGTTGCAA GAATACTCCA AATACCTCCA ACAGGCTTTT GAAAAATCCA CTAATGCAAG 120

TTTTACTCTT GGACACGGTT TCCAATTTGT CAGTTTGTCT TCACCTCTCC ACAACCACAC 180

TTTGTTTCCA GAAAAACAAA TATACACTAC GTCTCCTTTG GAGTGTGGTT TCGGCCAATC 240

TGTTACCTCA GTGTTGCCAT CTTCATTGCC AAAGCCTCCT TTTGGGATGT TGTTTGGATC 300

TCAGCCAGGT CTTTATTTGT CTGCTTTGGA TGCTACACAT CAGCAGTTGA CACCTTCCCA 360

GGAGCTGGAT GATCTGATAG ATTCTCAGAA GAACTTAGAG ACTTCATCAG CCTTCCAGTC 420

CTCATCTCAG AAATTGACTA GCCAGAAGGA ACAGAAAAAC TTAGAGTCTT CAACAGGCTT 480

TCAGATTCCA TCTCAGGAGT TAGCTAGCCA GATAGATCCT CAGAAAGACA TAGAGCCTAG 540

AACAACGTAT CAGATTGAGA ACTTTGCACA AGCGTTTGGT TCTCAGTTTA AGTCGGGCAG 600

CAGGGTGCCA ATGACCTTTA TCACTAACTC TAATGGAGAA GTGGACCATA GAGTAAGGAC 660

TTCAGTGTCA GATTTCTCAG GGTATACAAA TATGATGTCT GATGTAAGTG AGCCATGTAG 720

TACAAGAGTA AAGACACCCA CCAGCCAGAG TTACAGGTAA GGTCCCAAAA GTGGCCAGGC 780

TGGAGGTTTT TTAATGTAAT TTTGTTTTAT TTTGAGAACA CTGCCATTGG AATGTTTTTA 840

CACGATCCTA TTAAGAATAA TGTGATGCCC TTTCAATGCA ACTTTTCATA TTTAGTTTAT 900

TTTGTTAGCG TGATTTTAGC TCTGTTTGTA TTATGATTTT TAATCAAAAT CAATAGATTA 960

AAAATAGTTT GACATTCAAA GTGACAATGT TTAGCAATCA AATTTACATG TATAGATTGT 1020

CAGGGAATAG CCCAAATGTT TTAAACGCAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1080

AAAAAAAAAA AAAAAAA 1097

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 232 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
Met Leu Gln Glu Tyr Ser Lys Tyr Leu Gln Gln Ala Phe Glu Lys Ser
1               5                  10                  15

Thr Asn Ala Ser Phe Thr Leu Gly His Gly Phe Gln Phe Val Ser Leu
            20                  25                  30

Ser Ser Pro Leu His Asn His Thr Leu Phe Pro Glu Lys Gln Ile Tyr
        35                  40                  45

Thr Thr Ser Pro Leu Glu Cys Gly Phe Gly Gln Ser Val Thr Ser Val
    50                  55                  60

Leu Pro Ser Ser Leu Pro Lys Pro Pro Phe Gly Met Leu Phe Gly Ser
65                  70                  75                  80

Gln Pro Gly Leu Tyr Leu Ser Ala Leu Asp Ala Thr His Gln Gln Leu
                85                  90                  95

Thr Pro Ser Gln Glu Leu Asp Asp Leu Ile Asp Ser Gln Lys Asn Leu
            100                 105                 110

Glu Thr Ser Ser Ala Phe Gln Ser Ser Ser Gln Lys Leu Thr Ser Gln
        115                 120                 125

Lys Glu Gln Lys Asn Leu Glu Ser Ser Thr Gly Phe Gln Ile Pro Ser
    130                 135                 140

Gln Glu Leu Ala Ser Gln Ile Asp Pro Gln Lys Asp Ile Glu Pro Arg
145                 150                 155                 160

Thr Thr Tyr Gln Ile Glu Asn Phe Ala Gln Ala Phe Gly Ser Gln Phe
                165                 170                 175

Lys Ser Gly Ser Arg Val Pro Met Thr Phe Ile Thr Asn Ser Asn Gly
            180                 185                 190

Glu Val Asp His Arg Val Arg Thr Ser Val Ser Asp Phe Ser Gly Tyr
        195                 200                 205

Thr Asn Met Met Ser Asp Val Ser Glu Pro Cys Ser Thr Arg Val Lys
    210                 215                 220

Thr Pro Thr Ser Gln Ser Tyr Arg
225                 230
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 775 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GTGTCACATA CCACTCTTGT AGGTGTCCTC AATAATCCCC TTTTCCCACA AAATACACAG 60

GGTGTATTAT CTTTCTCTTT ATTCACCCCC ACTTTGCTGA ACTGAAGTTA ATTACATAGC 120

CTTTCTTCTA ACCTCCTTAG TAATGAACCT TCACATAAAG TGTATTTACA GCGTCTGTGG 180

TAGCCAGCCC TTCCTCCTCT ACTTTCTAGG AGGGGATAGC CAATAACTAG GAATTTAATG 240

ACAGATTTTT TTTTTCTTTG AAATAAATGG CCAGAGTTTC TCCATTTTAG AATTTTGTTG 300

TCCTCCTTAA TCATCTGCTT ACCTAGTCAT TACTCAATCT GCAGAAACTT CATAAAGGAA 360

AAGTGCTGCA TTGTTTTTAC AAATAACAGT TTGTAGGGAA AATATGACAA ACCTCAACTA 420

TGGGAGTTGT CCACAATACA AAATTTTGAA AAAACATTAC ATAGTGATAA TATCATACTT 480

GGTTGTTAGG CTTGTTGCTT CCCCACATCA GAGGCATCTA ATGATTTATC TTTTGTAATT 540

GCTGTGAACT TTTTTAAATA AGCCATTTAG TGTGAAATTG TCATGTATCA AATGGCTATT 600

GGAAATGGAC TTTACTCAAT TTTAATTCCA CTGCACTCTA GCCGGAGTGA CAGAGTAAGA 660

CTCTGTCTCA AAAATAAATA AATAAATAAA TAAATAAATA AATAAATAAA TAAATAAAAA 720

ATAATAATAC AAGTTTTCAT AAGGAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAA 775

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Met Thr Asn Leu Asn Tyr Gly Ser Cys Pro Gln Tyr Lys Ile Leu Lys
1 5 10 15

Lys His Tyr Ile Val Ile Ile Ser Tyr Leu Val Val Arg Leu Val Ala
20 25 30

Ser Pro His Gln Arg His Leu Met Ile Tyr Leu Leu
35 40

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2060 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

GAAAAAGAAG ACAAAGCTCA CCTTCAGGCG GAGGTGCAGC ACCTGCGAGA GGACAACCTG 60

AGGCTACAGG AGGAGTCCCA GAACGCCTCG GACAAGCTGA AGAAGTTCAC AGAATGGGTC 120

TTCAACACCA TAGACATGAG CTAGGGAAGG CTGAGGAGGA CAGGAGAAGG GCCCAGACAC 180

TCCCTCCAGT GAGTGTCCTG CAGCCCTTAT TCCCTCCATA GAAAGCATCC TCAGAGCACC 240

TTCCCTGGCT TCCTACTCTG CCCCCTTTCG GGGAGTGCAC AACACAATAG TTGCAGATCA 300

ACAATCATCA CCTGCCTTTT GTAGAAAAGA AAAACAAAAA AAGTAAATAA AAATTTTAAA 360

CAGTAAAATA AAAGTTTAAC TGCTAAAATG TGAATGTCTT TATTTTTTTG CACAATATCT 420

TTATCTGTTA TGTATTTAAG AAGAAACTGG GCCTTGGACC AGGGCGCCCC CTGGCCCATC 480

CGCCTCTATT CCCATCAGCT TTCTTATCAA CTTCAGGTAA CCCAAGCTTT CCCTTGTTAT 540

TCTAACAAAT ATCATTATTC CTAGAAAAAG AATGTTTTTA TAACTTGTTT GGGGAGTAGA 600

GAGGGATATT TCCTTACCTT CTTCCCTAAA ATGCCTGGAG AGGGAGTTGC TTTGAGAAAA 660

TGCCTACCTC CCTTGAATGA CTCGTGCATG AGCTAGTGCT GTCTGTACCT GTCCTCCAGA 720

GATCAGCAGG ACCGGAGTTA AATATTTAAC AGCAAGTCTG TAAACCAGAG CAGCTCTGAC 780

AGTGCCTGCA GGCCACACCC CTTCTCAGTC CTGCATTGTG AGGTCATTTC CTGCTTCTCC 840

CTTTCCCCAG GAAGATGGTC CCACTTGTGC TGCAAGACTC TTTTTTGTTT GGCTTAATTG 900

AGCCCCACTA AATTGGAATC AATCTCTCTT ACAGCTTCCT GGCTCCAAAC ATTAATTGAT 960

TTCAGAATTC CCCCAAACTA AAACCTTATC TGTCTGCATT TTGAATGCAT TTTGGTCAAA 1020

AGTATACGTT TTAAAGATTT TTAAAGATAA AAATGTGGCA CAACTGGTTT TTTTAGCTTG 1080

CTGAAAATGA CCATATCTCT AAATTAATCT TTCTCTCCAG AGCAAGACTT CACCAGTATT 1140

TGTAACTAGG AGAAGCTAAG TGAATGTTTA ATTGTGAATT TTAATCATTG CTTGTTAGGA 1200

ATAATGACTG TGATACTAGA ATGGGCTTTT GAAACCTGCA TGTCCCAGTG TGAAATTTCA 1260

GCACGGCATT TTCTGCATCC TTTCATGGCC ATCCAAAGGA TTCCGCTGCA GAAATTATTG 1320

ATGTGCTATT TTTGCTGTCT TGTGATGCAG GCTGCTTTGG GCCCCTGGGT CACTCTTCCA 1380

AGGCTGCTGT AGAGCACAGA GACATGGGGC TGGCCAGTGT TGACTGACCT GAGGAGACCC 1440

CTTTGTTTGT TGCCTTCATA ACTGTCACTA AACCGACCCC TCTGCCCTTT CAGTGGCAAC 1500

TCTGGTCTAA GGGAACATTC AGCACTCTAG CGGCATCTGA TTGGAAGTTC CCTCACCCAA 1560

GTAATCTCAA TTCCTTCCTC TCTCCATCCC TGAAAGAAAC AGGATGGATT TTCCTCTCTT 1620

CTCCCTGCTA CATTCACTAC CAGATTTTTA TGCTACAGTT TCATTCTTGA TTGTGATTTC 1680

TCCATGGAAT TTTTTTTTTC TGGTGACATT TCTATCATGG AAATAGGAAG ATTTCGGAGT 1740

GCTTTGTGAA GATTTCAATT GTCTGTCTCT TTCTCTCTTT GACTTGTATG AAGGAGATTG 1800

TACATTGCCT GATATCTCTT TGTAAATGAG AAATATTGCT AACATCCAAG CATTCTGAAG 1860

TCTTGCTTAT CCTTCTGAGT TTAGTTCTCA TTTTGTTTTA CATTTTGTTT GGGGACTTGG 1920

GGCAAGCTAT TTATTAGAGT TTTGCAACAG AGTTCTTGTT TGAAGCCTCT AAAGACTACC 1980

TGTAAAATTC AAAGAATAAA ATTCATTTTA AACGCTCTTT TAAAAAAAAA AAAAAAAAAA 2040

AAAAAAAAAA AAAAAAAAAA 2060

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 62 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Met Thr Val Ile Leu Glu Trp Ala Phe Glu Thr Cys Met Ser Gln Cys
1 5 10 15

Glu Ile Ser Ala Arg His Phe Leu His Pro Phe Met Ala Ile Gln Arg
20 25 30

Ile Pro Leu Gln Lys Leu Leu Met Cys Tyr Phe Cys Cys Leu Val Met
35 40 45

Gln Ala Ala Leu Gly Pro Trp Val Thr Leu Pro Arg Leu Leu
50 55 60

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1160 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GATTATTTTC AGTAGGCAGA CATCTAATCG GAATCTTGCT CTTGTTGCCC AGGCTGGAGT 60

GTAATGGCAC AATCTCGGCT TACTGCAACC TCTGCCTCCT GGATTCAAGT GATTCTCCTG 120

CCTCAGCCTC CCAAGTAGCT GGGATTACAG CCCTGAAAAC CACTCGCTTG CAGAGCGCTG 180

GATCAGCAAT GCCTACTAGT TCTTCATTCA AACACCGGAT TAAAGAGCAG GAAGACTACA 240

TCCGAGATTG GACTGCTCAT CGAGAAGAGA TAGCCAGGAT CAGCCAAGAT CTTGCTCTCA 300

TTGCTCGGGA GATCAACGAT GTAGCAGGAG AGATAGATTC AGTGACTTCA TCAGGCACTG 360

CCCCTAGTAC CACAGTAAGC ACTGCTGCCA CCACCCCTGG CTCTGCCATA GACACTAGAG 420

AAGAGTTGGT TGATCGTGTT TTTGATGAAA GCCTCAACTT CCAAAAGATT CCTCCATTAG 480

TTCATTCCAA AACACCAGAA GGAAACAACG GTCGATCTGG TGATCCAAGA CCTCAAGCAG 540

CAGAGCCTCC CGATCACTTA ACAATTACAA GGCGGAGAAC CTGGAGCAGG GATGAAGTCA 600

TGGGAGATAA TCTGCTGCTG TCATCCGTCT TTCAGTTCTC TARGAAGATA AGACAATCTA 660

TAGATAAGAC AGCTGGAAAG ATCAGAATAT TATTTAAAGA CAAAGATCGG AATTGGGATG 720

ACATAGAAAG CAAATTAAGA GCCGAAAGTG AAGTCCCTAT TGTGAAAACC TCGAGCATGG 780

AGATTTCTTC TATCTTACAG GAACTGAAAA GAGTAGAAAA GCAGCTACAA GCAATCAATG 840

CTATGATTGA TCCTGATGGA ACTTTGGAGG CTCTGAACAA CATGGGATTT CCCAGTGCTA 900

TGTTGCCATC TCCACCGAAA CAGAAGTCCA GCCCTGTGAA TAACCACCAC AGCCCGGGTC 960

AGACACCAAC ACTTGGCCAA CCAGAAGCTA GGGCTCTTCA TCCTGCTGCT GTTTCAGCCG 1020

CAGCTGAATT TGAGAATGCT GAATCTGAGG CTGATTTCAG TATACATTTC AATAGAGTCA 1080

ACCCTGATGG GGAAGAGGAA GATGTTACAG TAACATAAAT GACTTTCTCT TGATTGTTGA 1140

AAAAAAAAAA AAAAAAAAAA 1160

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 309 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Met Pro Thr Ser Ser Ser Phe Lys His Arg Ile Lys Glu Gln Glu Asp
1 5 10 15

Tyr Ile Arg Asp Trp Thr Ala His Arg Glu Glu Ile Ala Arg Ile Ser
20 25 30

Gln Asp Leu Ala Leu Ile Ala Arg Glu Ile Asn Asp Val Ala Gly Glu
35 40 45

Ile Asp Ser Val Thr Ser Ser Gly Thr Ala Pro Ser Thr Thr Val Ser
50 55 60

Thr Ala Ala Thr Thr Pro Gly Ser Ala Ile Asp Thr Arg Glu Glu Leu
65 70 75 80

Val Asp Arg Val Phe Asp Glu Ser Leu Asn Phe Gln Lys Ile Pro Pro
85 90 95

Leu Val His Ser Lys Thr Pro Glu Gly Asn Asn Gly Arg Ser Gly Asp
100 105 110

Pro Arg Pro Gln Ala Ala Glu Pro Pro Asp His Leu Thr Ile Thr Arg
115 120 125

Arg Arg Thr Trp Ser Arg Asp Glu Val Met Gly Asp Asn Leu Leu Leu
130 135 140

Ser Ser Val Phe Gln Phe Ser Xaa Lys Ile Arg Gln Ser Ile Asp Lys
145 150 155 160

Thr Ala Gly Lys Ile Arg Ile Leu Phe Lys Asp Lys Asp Arg Asn Trp
165 170 175

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Asp Asp Ile Glu Ser Lys Leu Arg Ala Glu Ser Glu Val Pro Ile Val
            180                 185                 190

Lys Thr Ser Ser Met Glu Ile Ser Ser Ile Leu Gln Glu Leu Lys Arg
        195                 200                 205

Val Glu Lys Gln Leu Gln Ala Ile Asn Ala Met Ile Asp Pro Asp Gly
    210                 215                 220

Thr Leu Glu Ala Leu Asn Asn Met Gly Phe Pro Ser Ala Met Leu Pro
225                 230                 235                 240

Ser Pro Pro Lys Gln Lys Ser Ser Pro Val Asn Asn His His Ser Pro
                245                 250                 255

Gly Gln Thr Pro Thr Leu Gly Gln Pro Glu Ala Arg Ala Leu His Pro
            260                 265                 270

Ala Ala Val Ser Ala Ala Ala Glu Phe Glu Asn Ala Glu Ser Glu Ala
        275                 280                 285

Asp Phe Ser Ile His Phe Asn Arg Val Asn Pro Asp Gly Glu Glu Glu
    290                 295                 300

Asp Val Thr Val Thr
305
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1536 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
GAAGAGAGAA AATCAGCCTG TCTGCTCTCT CCTTGGCTCA ACAAGGCCTC TAACAGTCTT     60

CTGTCCTCTA TTCTGCACAC GGCATATTTG GGAACGAGAA ACAAAAGTTT TCCCAAATGA    120

AGAGAACTCA CTTGTTTATT GTGGGGATTT ATTTTCTGTC CTCTTGCAGG GCAGAAGAGG    180

GGCTTAATTT CCCCACATAT GATGGGAAGG ACCGAGTGGT AAGTCTTTCC GAGAAGAACT    240

TCAAGCAGGT TTTAAAGAAA TATGACTTGC TTTGCCTCTA CTACCATGAG CCGGTGTCTT    300

CAGATAAGGT CACGCANAAA CAGTTCCAAC TGAAAGAAAT CGTGCTTGAG CTTGTGGCCC    360

ACGTCCTTGA ACATAAAGCT ATAGGCTTTG TGATGGTGGA TGCCAAGAAA GAAGCCAAGC    420
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TTGCCAAGAA ACTGGGTTTT GATGAAGAAG GAAGCCTGTA TATTCTTAAG GGTGATCGCA 480

CAATAGAGTT TGATGGCGAG TTTGCAGCTG ATGTCTTGGT GGAGTTCCTC TTGGATCTAA 540

TTGAAGACCC AGTGGAGATC ATCAGCAGCA AACTGGAAGT CCAAGCCTTC GAACGCATTG 600

AAGACTACAT CAAACTCATT GGCTTTTTCA AGAGTGAGGA CTCAGAATAC TACAAGGCTT 660

TTGAAGAAGC AGCTGAACAC TTCCAGCCTT ACATCAAATT CTTTGCCACC TTTGACAAAG 720

GGGTTGCAAA GAAATTATCT TTGAAGATGA ATGAGGTTGA CTTCTATGAG CCATTTATGG 780

ATGAGCCCAT TGCCATCCCC AACAAACCTT ACACAGAAGA GGAGCTGGTG GAGTTTGTGA 840

AGGAACACCA AAGGTGCCTG AGATGGCATG TGGGGGCTGG GGGCCTGGGG TCTGGGGAAT 900

GGAGAGGAGC CTCTCTGTGC TAACATTTCA GACCTGCCAA GAGCAACAAC CTAGTTAGTA 960

CCCCAGCAGT ACAGAACTCA GTAGTATGGC TTTGTTGATC AGTAATGACT AGCAGGGATG 1020

TTATTACTTC TGAATCTAAG TCTGCACCTG CAAGCAGAGT TTGATAAATC CCTCAGTCAG 1080

CAAATCCCCT CAAAGCCAGG GCAAGATATA AATAAAATTC TATACTAGGA ATGAGAGCAA 1140

TTTAGTGAAA GTTCCCATAT ACCAATAACC ATGCCCAGTG CTTTAGGGAA ACTATTTTAT 1200

CTAATCTCCA ACCTTAGGGA GTAATTATTA TTATCCCAAT TTTACAGATC AAGGAATTGG 1260

ACTCAATAGT TAAGTAACTT AGCCAAGGAT GAACACTCTA TGCATAGAAC TTCTGGGAGA 1320

GAAATGCTTG ATACCACTTA GTGTAGCTCC AGCATGGATC AGCAAACTTT TTCTGTAAAG 1380

AACAAAATGG TAAATATTTC AGGTTCTGTG GGCCAGATGG CGTCTGTAGC AACTACTTAA 1440

CTGCGGCTGT GGCATGAAAG CAGCCATGGA TCATGTATAA ACAAATGGGT GTGGCTGTGT 1500

ACCAGTAAAA GTTTATTTAG GAAAAAAAAA AAAAAA 1536

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 268 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Met Lys Arg Thr His Leu Phe Ile Val Gly Ile Tyr Phe Leu Ser Ser
1 5 10 15

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Cys Arg Ala Glu Glu Gly Leu Asn Phe Pro Thr Tyr Asp Gly Lys Asp
            20                  25                  30

Arg Val Val Ser Leu Ser Glu Lys Asn Phe Lys Gln Val Leu Lys Lys
        35                  40                  45

Tyr Asp Leu Leu Cys Leu Tyr Tyr His Glu Pro Val Ser Ser Asp Lys
    50                  55                  60

Val Thr Xaa Lys Gln Phe Gln Leu Lys Glu Ile Val Leu Glu Leu Val
65                  70                  75                  80

Ala His Val Leu Glu His Lys Ala Ile Gly Phe Val Met Val Asp Ala
                85                  90                  95

Lys Lys Glu Ala Lys Leu Ala Lys Lys Leu Gly Phe Asp Glu Glu Gly
            100                 105                 110

Ser Leu Tyr Ile Leu Lys Gly Asp Arg Thr Ile Glu Phe Asp Gly Glu
        115                 120                 125

Phe Ala Ala Asp Val Leu Val Glu Phe Leu Leu Asp Leu Ile Glu Asp
    130                 135                 140

Pro Val Glu Ile Ile Ser Ser Lys Leu Glu Val Gln Ala Phe Glu Arg
145                 150                 155                 160

Ile Glu Asp Tyr Ile Lys Leu Ile Gly Phe Phe Lys Ser Glu Asp Ser
                165                 170                 175

Glu Tyr Tyr Lys Ala Phe Glu Glu Ala Ala Glu His Phe Gln Pro Tyr
            180                 185                 190

Ile Lys Phe Phe Ala Thr Phe Asp Lys Gly Val Ala Lys Lys Leu Ser
        195                 200                 205

Leu Lys Met Asn Glu Val Asp Phe Tyr Glu Pro Phe Met Asp Glu Pro
    210                 215                 220

Ile Ala Ile Pro Asn Lys Pro Tyr Thr Glu Glu Glu Leu Val Glu Phe
225                 230                 235                 240

Val Lys Glu His Gln Arg Cys Leu Arg Trp His Val Gly Ala Gly Gly
                245                 250                 255

Leu Gly Ser Gly Glu Trp Arg Gly Ala Ser Leu Cys
            260                 265
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1009 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

GAATTCGGCC TTCATGCGCC TGCAGGAAAG AATCTGACAT CATCACACTG TGTTTTCCTT 60

AACTTGACAG GAAGTCAACT TCAAGCAGAT TGACTTGAAA CGGGATCTCA TTTAGGAAGC 120

ATAAGTGTCC AATCAAAAAC TGTGTATTTT TTTAAATTTG GAAAATACTC AAGTTCCAGT 180

TGCTTATCAT TCTCCTTCAC TTTCTGAAAA CCTGGCAATC CCATGTGGAC TTCTGGTAGA 240

ATGAGCAATG CAAAGAACTG GCTTGGACTT GGCATGTCCT TGTACTTCTG GGGGCTGATG 300

GACCTTACGA CCACCGTTCT CTCGGACACC CCAACACCAC AAGGTGAATT AGAAGCACTC 360

CTGTCAGACA AGCCACAGTC ACATCAGCGG ACCAAGARGA GCTGGGTTTG GAACCAGTTT 420

TTCGTTCTGG AAGAGTACAC TGGGACCGAC CCTTTGTATG TCGGCAAGGT AAGAAATGCC 480

AAGTAGAAAT GACCCGGGTA GTGGATATTG AAATTGAATA TGAATTGAGT ATCAAAGTTG 540

ACCTAGCCTT TATYTGAGAC CTGAGAAAAA CTAGAACAAG TGGTACGTTA CTTGACACCT 600

AGCTAAAATG TAACTTCTGC TTTGTCAGAG ACCAGTCTGA AAGGAAAGAT TTATTTCCTT 660

GTCCATGTCT CTGGTATGAA TGGGAAAAAG TGGGAATTGG GATTTGGAGG AAAAGGCTCA 720

GACCCTGCAA GAGCTATTCA AGTCCTAAAA GAGGCAGCAG CAGCTGTCTG GGAATGACAG 780

AATGGGGGAG AGGGAAACTT GGAAATACAA GAAGAGTACA GAGTTTTTTG CTTTGTGTTT 840

TTATGGGGTT TTTTTCAGAG CATTTCCAGA GGTATTGCCT GAGGTGCAAA TTTAATGAAA 900

AAAATAAAAA TAAAACATTT TTCATTTCAG AAGATCTTAG CATGTGCTTT AGGATAGTTG 960

GAGACAATAA ATATATTTAT AAATGTTAAA AAAAAAAAA AAAAAAAAA 1009

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Met Trp Thr Ser Gly Arg Met Ser Asn Ala Lys Asn Trp Leu Gly Leu
1 5 10 15

Gly Met Ser Leu Tyr Phe Trp Gly Leu Met Asp Leu Thr Thr Thr Val
20 25 30

Leu Ser Asp Thr Pro Thr Pro Gln Gly Glu Leu Glu Ala Leu Leu Ser
35 40 45

Asp Lys Pro Gln Ser His Gln Arg Thr Lys Xaa Ser Trp Val Trp Asn
50 55 60

Gln Phe Phe Val Leu Glu Glu Tyr Thr Gly Thr Asp Pro Leu Tyr Val
65 70 75 80

Gly Lys Val Arg Asn Ala Lys
85

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2546 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

AAAAGAAACC AAGGAAATTT GTATGATAAG GCAGGTAAAG TGAGGAAACA TGCAACTGAA 60

CAGGAAAAAA CTGAAGAGGG ATTAGGCCCT AATATAAAAA GCATTGTCAC CATGTTGATG 120

CTGATGCTAT TGATGATGTT TGCTGTCCAC TGTACCTGGG TCACAAGCAA TGCCTACTCT 180

AGTCCAAGTG TAGTCCTGGC CTCATACAAT CATGATGGCA CCAGGAATAT CTTAGATGAT 240

TTTAGAGAAG CTTACTTTTG GCTAAGGCAA AATACAGATG AACATGCACG AGTAATGTCT 300

TGGTGGGATT ATGGCTATCA GATAGCTGGA ATGGCTAATA GAACTACGTT GGTGGATAAT 360

AACACCTGGA ATAACAGCCA CATAGCACTG GTGGGAAAAG CTATGTCTTC TAATGAAACA 420

GCAGCCTATA AAATCATGAG GACTCTAGAT GTAGATTATG TTTTGGTTAT TTTTGGAGGG 480

GTTATTGGCT ATTCTGGTGA TGATATCAAC AAATTTCTCT GGATGGTTAG GATAGCTGAA 540

GGAGAACATC CCAAAGACAT TCGGGAAAGT GACTATTTTA CCCCACAGGG AGAATTCCGT 600

GTAGACAAAG CAGGATCCCC TACTTTGTTG AATTGCCTTA TGTATAAAAT GTCATACTAC 660

AGATTTGGAG AAATGCAGCT GGATTTTCGT ACACCCCCAG GTTTTGACCG AACACGTAAT 720

GCTGAGATTG GAAATAAGGA CATTAAATTC AAACATTTGG AAGAAGCCTT TACATCAGAA 780

CACTGGCTTG TTAGGATATA TAAAGTAAAA GCACCTGATA ACAGGGAGAC ATTAGATCAC 840

AAACCTCGAG TCACCAACAT TTTCCCAAAA CAGAAGTATT TGTCAAAGAA GACTACCAAA 900

AGGAAGCGTG GCTACATTAA AAATAAGCTG GTTTTTAAGA AAGGCAAGAA AATATCTAAG 960

AAGACTGTTT AAATGCACTG TTCTGGTTCC TAACTTGAAG CAGTTGTCCT TGTGAGAACC 1020

GGTCTTTGCC TTTAGCTCAT GTCGTGTTTC ACAGCAAAGA GGGTACAGAA CCATCACTGG 1080

TCCAGGTTAA TGTACAAAAT TTTCTGGCAA TGCCTGATTA AAAAAATAAA ATTGGCTTGT 1140

TGAGAACAGC TGTTTTCGAT TTCTAATGTG AAGCAAGACA GAGCACTGCT GTAAATGTCT 1200

AGCAGCAGAT TTTTTTTTTA TTGGTACATA TTATCCTTCA AATCTGAGAA TTTGGACTAA 1260

CTGCACCAAA GAACCCTCTA ATTTGGTCCC TGGCACATGC ATACTTGTCA ATGTTTTTAT 1320

TCTCTTACAA GACCTGCATT TTATTTGAAT TACCCGAATA GCAATATGTA AAATACAAGT 1380

GACAAAATGT GATGAGAGCT TCTTGAACCG GTAAACTAGT ACAGGTCTGA GAAAGACATA 1440

TTAGAAGAAT CATTATACTT CCCTGAATTA TATTTATTTT CATGTTTCTC TAATGCAAAG 1500

AATGTTTCAT CAAATGTATA TTTTCTGTTG CTTACTGTTT GCTCTGAGAA GAAGCTGCTG 1560

TTTCAAAGAT GGACCTCTGA GTAGCTAATT GATTCAAGTA GTTTTTTTAT GTTGACACAT 1620

TATTACTGCT GTTAGCAGTC GTTTTCACCA GGTACTTACA GAGCAGATTT CATACATCAT 1680

TCATTCAAGG GCTAAATTTA TATTTTTTGG AAATCATGGC AACTACACAG GATGTTGCTT 1740

ACCAGGACGG AGTTTTGGTA TCTTAGTACT GAAGTTAGCA CTATGTTTAC ATGCAAAAGA 1800

TTAAGGAAAA AACCCTTAAA GTGGACAGGT ATCCAAAGTT CATTTTCTGT GACTCATCAA 1860

AGTGACAAAA GACTTGTAAC AACTTTGCCT GGACTTTTTT CATTTTACAA CAGTTCATCC 1920

ATTCACAATG ATTTTGTTCT CTGCTCCATA TTTTTTAATC CCTTAAGCAT TTGATGAAAC 1980

ACTCTTTAGT GCTATATGCA TTTTCTTACT TTTGTTAAAA ATGTGACAAT TGTCAAAAAA 2040

TGCACTAAAA TGTAAATGGA GATTGAACAA GTTCACTTTC CAGCTTATAG GCAACTTTAT 2100

ACAGACTTGA ACATTTTCTC CAGTTGTTTA GTAAAAGTGA AAGAGAAAGG GTTTTTCCTG 2160

CCACAGGATA TAACTTTTTT TTATATAACA AGCATAACAC ACCACTGCTT TTGGTGGAAA 2220

AGTGCAGAAT AGTATGTACC TTTTATGAAG AAAAATGTAA TTTACAATAT TCAGTGAGAA 2280

TGTTACTGCT GATTTTCTTT TCCAAGGTGT AGAATATTCT TTGATTTATA GAATTCATTT 2340

TTGACCCAGA TGATGGTTCC TTTACAGAAC AATAAAATGG CTGAACATTT TCACAAATAG 2400

AGTGTAACGA AGTCTGGATT TCTGATACCT TGTCATTTGG GGGATTTTAT TTTACTTTGT 2460

TGCTTTAAAA TTCAATGCAG AGAAGTTGTT GACTGTAGGG GAAATAAAGT TAATTCAAAT 2520

TTTGAAAAAA AAAAAAAAAA AAAAAA 2546

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 286 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Met Leu Met Leu Met Leu Leu Met Met Phe Ala Val His Cys Thr Trp
1 5 10 15

Val Thr Ser Asn Ala Tyr Ser Ser Pro Ser Val Val Leu Ala Ser Tyr
20 25 30

Asn His Asp Gly Thr Arg Asn Ile Leu Asp Asp Phe Arg Glu Ala Tyr
35 40 45

Phe Trp Leu Arg Gln Asn Thr Asp Glu His Ala Arg Val Met Ser Trp
50 55 60

Trp Asp Tyr Gly Tyr Gln Ile Ala Gly Met Ala Asn Arg Thr Thr Leu
65 70 75 80

Val Asp Asn Asn Thr Trp Asn Asn Ser His Ile Ala Leu Val Gly Lys
85 90 95

Ala Met Ser Ser Asn Glu Thr Ala Ala Tyr Lys Ile Met Arg Thr Leu
100 105 110

Asp Val Asp Tyr Val Leu Val Ile Phe Gly Gly Val Ile Gly Tyr Ser
115 120 125

Gly Asp Asp Ile Asn Lys Phe Leu Trp Met Val Arg Ile Ala Glu Gly
130 135 140

Glu His Pro Lys Asp Ile Arg Glu Ser Asp Tyr Phe Thr Pro Gln Gly
145 150 155 160

Glu Phe Arg Val Asp Lys Ala Gly Ser Pro Thr Leu Leu Asn Cys Leu
165 170 175

Met Tyr Lys Met Ser Tyr Tyr Arg Phe Gly Glu Met Gln Leu Asp Phe
180 185 190

Arg Thr Pro Pro Gly Phe Asp Arg Thr Arg Asn Ala Glu Ile Gly Asn
195 200 205

Lys Asp Ile Lys Phe Lys His Leu Glu Glu Ala Phe Thr Ser Glu His
210 215 220

Trp Leu Val Arg Ile Tyr Lys Val Lys Ala Pro Asp Asn Arg Glu Thr
225 230 235 240

Leu Asp His Lys Pro Arg Val Thr Asn Ile Phe Pro Lys Gln Lys Tyr
245 250 255

Leu Ser Lys Lys Thr Thr Lys Arg Lys Arg Gly Tyr Ile Lys Asn Lys
260 265 270

Leu Val Phe Lys Lys Gly Lys Lys Ile Ser Lys Lys Thr Val
275 280 285

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4061 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

AAGCAATTGA AGAAATTGCA GCAGGATGTG ATGGAAATGA AAAAAACAAA GGTTCGCCTA 60

ATGAAACAAA TGAAAGAAGA ACAAGAGAAA GCCAGACTGA CTGAGTCTAG AAGAAACAGA 120

GAGATTGCTC AGTTGAAAAA GGATCAACGT AAAAGAGATC ATCMACTTAG ACTTCTGGAA 180

GCCCAAAAAA GAAACCAAGA AGTGGTTCTA CGTCGCAAAA CTGAAGAGGT TACGGCTCTT 240

CGTCGGCAAG TAAGACCCAT GTCAGATAAA GTGGCTGGGA AAGTTACTCG GAAGCTGAGT 300

TCATCTGATG CACCTGCTCA GGACACAGGT TCCAGTGCAG CTGCTGTCGA AACAGATGCA 360

TCAAGGACAG GAGCCCAGCA GAAAATGAGA ATTCCTGTGG CGAGAGTCCA GGCCTTACCA 420

ACGCCGGCAA CAAATGGAAA CAGGAAAAAA TATCAGAGGA AAGGATTGAC TGGCCGAGTG 480

TTTATTTCCA AGACAGCTCG CATGAAGTGG CAGCTCCTTG AGCGCAGGGT CACAGACATC 540

ATCATGCAGA AGATGACCAT TTCCAACATG GAGGCAGATA TGAATAGACT CCTCAAGCAA 600

CGGGAGGAAC TCACAAAAAG ACGAGAGAAA CTTTCAAAAA GAAGGGAGAA GATAGTCAAG 660

GAGAATGGAG AGGGAGATAA AAATGTGGCT AATATCAATG AAGAGATGGA GTCACTGACT 720

GCTAATATCG ATTACATCAA TGACAGTATT TCTGATTGTC AGGCCAACAT AATGCAGATG 780

GAAGAAGCAA AGGAAGAAGG TGAGACATTG GATGTTACTG CAGTCATTAA TGCCTGCACC 840

CTTACAGAAG CCCGATACCT GCTAGATCAC TTCCTGTCAA TGGGCATCAA TAAGGGTCTT 900

CAGGCTGCCC AGAAAGAGGC TCAAATTAAA GTACTGGAAG GTCGACTCAA ACAAACAGAA 960

ATAACCAGTG CTACCCAAAA CCAGCTCTTA TTCCATATGT TGAAAGAGAA GGCAGAATTA 1020

AATCCTGAGC TAGATGCTTT ACTAGGCCAT GCTTTACAAG ATCTAGATAG CGTACCATTA 1080

GAAAATGTAG AGGATAGTAC TGATGAGGAT GCTCCTTTAA ACAGCCCAGG ATCAGAAGGA 1140

AGCACGCTGT CTTCAGATCT CATGAAGCTT TGTGGTGAAG TGAAACCTAA GAACAAGGCC 1200

CGAAGGAGAA CCACCACTCA GATGGAATTG CTGTATGCAG ATAGCAGTGA ACTAGCTTCA 1260

GACACTAGTA CAGGAGATGC CTCCTTGCCT GGCCCTCTCA CACCTGTTGC AGAAGGGCAA 1320

GAGATTGGAA TGAATACAGA GACAAGTGGT ACTTCTGCTA GGGAAAAAGA GCTCTCTCCC 1380

CCACCTGGCT TACCTTCTAA GATAGGCAGC ATTTCCAGGC AGTCATCTCT ATCAGAAAAA 1440

AAAATTCCAG AGCCTTCTCC TGTAACAAGG AGAAAGGCAT ATGAGAAAGC AGAAAAATCA 1500

AAGGCCAAGG AACAAAAGCA CTCAGATTCT GGAACTTCAG AGGCTAGTCT TTCACCTCCT 1560

TCTTCCCCAC CAAGCCGGCC CCGTAATGAA CTGAATGTTT TTAATCGTCT TACTGTTTCT 1620

CAGGGAAACA CATCAGTTCA GCAGGATAAG TCTGATGAAA GTGACTCCTC TCTCTCGGAG 1680

GTACACAGCA GATCCTCCAG AAGGGGCATA ATCAACCCAT TTCCTGCTTC AAAAGGAATC 1740

AGAGCTTTTC CACTTCAGTG TATTCACATA GCTGAAGGGC ATACAAAAGC TGTGCTCTGT 1800

GTGGATTCTA CTGATGATCT CCTCTTCACT GGATCAAAAG ATCGTACTTG TAAAGTATGG 1860

AATCTGGTGA CTGGGCAGGA AATAATGTCA CTGGGGGGTC ATCCCAACAA TGTCGTGTCT 1920

GTAAAATACT GTAATTATAC CAGTTTGGTC TTCACTGTAT CAACATCTTA TATTAAGGTG 1980

TGGGATATCA GAGATTCAGC AAAGTGCATT CGAACACTAA CGTCTTCAGG TCAAGTTACT 2040

CTTGGAGATG CTTGTTCTGC AAGTACCAGT CGAACAGTAG CTATTCCTTC TGGAGAGAAC 2100

CAGATCAATC AAATTGCCCT AAACCCAACT GGCACCTTCC TCTATGCTGC TTCTGGAAAT 2160

GCTGTCAGGA TGTGGGATCT TAAAAGGTTT CAGTCTACAG GAAAGTTAAC AGGACACCTA 2220

GGCCCTGTTA TGTGCCTTAC TGTGGATCAG ATTTCCAGTG GACAAGATCT AATCATCACT 2280

GGCTCCAAGG ATCATTACAT CAAAATGTTT GATGTTACAG AAGGAGCTCT TGGGACTGTG 2340

AGTCCCACCC ACAATTTTGA ACCCCCTCAT TATGATGGCA TAGAAGCACT AACCATTCAA 2400

GGGGATAACC TATTTAGTGG GTCTAGAGAT AATGGAATCA AGAAATGGGA CTTAACTCAA 2460

AAAGACCTTC TTCAGCAAGT TCCAAATGCA CATAAGGATT GGGTCTGTGC CCTGGGAGTG 2520

GTGCCAGACC ACCCAGTTTT GCTCAGTGGC TGCAGAGGGG GCATTTTGAA AGTCTGGAAC 2580

ATGGATACTT TTATGCCAGT GGGAGAGATG AAGGGTCATG ATAGTCCTAT CAATGCCATA 2640

TGTGTTAATT CCACCCACAT TTTTACTGCA GCTGATGATC GAACTGTGAG AATTTGGAAG 2700

GCTCGCAATT TGCAAGATGG TCAGATCTCT GACACAGGAG ATCTGGGGGA AGATATTGCC 2760

AGTAATTAAA CATGAATGAA GATAGGTTGT AAACTGAATG CTGTGATAAT ACTCTGTATT 2820

CTTTATGGAA AATGTTGTCC TGTACTTACT AGGCAAAACG TATGAATCGG ATTAACTGGA 2880

AAATATATCT GAATTCAACT GCTGACTATA AATGGTATTC TAATAAAATT GTGTACTATC 2940

CTGTGTGCTT AGTTTTAAGA TCAACCAATA GATATATATC CTACAATTGA TATATTGCTT 3000

TATTCACACT TTTATTGTGG CTGAATTTTT GTGCCTATCT ATAAAACACA CTTTCAAATT 3060

ATTTGAATTA CCAAGACGTC TGCTTTTGTG ACAGTCAGAA AACACACCTG GAATACGATG 3120

CAGCCCACCA TTAACTCATT CATGTAGTTT ATTCAAGTGA TTTATGTATT TAAACTAAAT 3180

ATTGAAAATG TTAGTCAAAT TGTGGTTTGC TTGTCAGGTA TTTATATCAG TCTGTAGTGG 3240

ATTCCCAAAT TTCAAAGCTC TTTTAATGTA ATGGACAAAA ATAAGATATG AGAATATTAT 3300

TGATGAATTT TCATAAGGTG GAATTGATCT TAATCTACTA ACAGAGAAGG GTAGACAGTT 3360

TGTGTTAAAT GTTGGCATTT ACTTGTATTG ACCAAAGTTT TGCAGCTCTA CTATATTCTG 3420

TGCTCAGGAC TAAAATGCTG TTAATTTTTT TTTTTTTTTT TCCAGTGCTG TGCATATATT 3480

CTGTGATGGG AAACATTGTT GATGTCCTAA CAGAAATATA TTTTGATCTA TTTTCCTATG 3540

GAGTTGTTTC TATTATGACC ATTTAATTTT GTTTTTATTT AATAGTAGTA TTTCCTTCCC 3600

TTTTATCTAA TTTTTTATAT GCTGCTAAAT ATATTTTAAA TATACTATGT TTGCGAACCT 3660

TGGTAGCTAT GATGAGAGCT ATTATCATCT GTGGTGGGAA AAGCTATGTA AATAGGTAGA 3720

TTGTATAGAG AGACTATCTT GTGTTGTGCC TGTATGAATT TTTAAAAGTT GTTGACTGGA 3780

TTTTGCAAAA GGATGTATAA TATTTCTGTC TGCTCAGAAT ATTAATTTGT AAATTCTGCA 3840

AGTTTAATTT TTATGTAGAT GGTATAACAT TTGAAAATAT TGTCTTATGT GATTTTTTCC 3900

CCTGAAAATA TTTGCTTGTA AATGAAAACT TAGCTAGGGC TTAAATAAAC ATGTTGCTAT 3960

GAAATKRAAA AAAAAAAAAA AAAARAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 4020

AARAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA A 4061

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 910 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Met Lys Lys Thr Lys Val Arg Leu Met Lys Gln Met Lys Glu Glu Gln
1 5 10 15

Glu Lys Ala Arg Leu Thr Glu Ser Arg Arg Asn Arg Glu Ile Ala Gln
20 25 30

Leu Lys Lys Asp Gln Arg Lys Arg Asp His Xaa Leu Arg Leu Leu Glu
35 40 45

Ala Gln Lys Arg Asn Gln Glu Val Val Leu Arg Arg Lys Thr Glu Glu
50 55 60

Val Thr Ala Leu Arg Arg Gln Val Arg Pro Met Ser Asp Lys Val Ala
65 70 75 80

Gly Lys Val Thr Arg Lys Leu Ser Ser Ser Asp Ala Pro Ala Gln Asp
85 90 95

Thr Gly Ser Ser Ala Ala Ala Val Glu Thr Asp Ala Ser Arg Thr Gly
100 105 110

Ala Gln Gln Lys Met Arg Ile Pro Val Ala Arg Val Gln Ala Leu Pro
115 120 125

Thr Pro Ala Thr Asn Gly Asn Arg Lys Lys Tyr Gln Arg Lys Gly Leu
130 135 140

Thr Gly Arg Val Phe Ile Ser Lys Thr Ala Arg Met Lys Trp Gln Leu
145 150 155 160

Leu Glu Arg Arg Val Thr Asp Ile Ile Met Gln Lys Met Thr Ile Ser
165 170 175

Asn Met Glu Ala Asp Met Asn Arg Leu Leu Lys Gln Arg Glu Glu Leu
180 185 190

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Thr Lys Arg Arg Glu Lys Leu Ser Lys Arg Arg Glu Lys Ile Val Lys
        195                 200                 205

Glu Asn Gly Glu Gly Asp Lys Asn Val Ala Asn Ile Asn Glu Glu Met
    210                 215                 220

Glu Ser Leu Thr Ala Asn Ile Asp Tyr Ile Asn Asp Ser Ile Ser Asp
225                 230                 235                 240

Cys Gln Ala Asn Ile Met Gln Met Glu Glu Ala Lys Glu Glu Gly Glu
                245                 250                 255

Thr Leu Asp Val Thr Ala Val Ile Asn Ala Cys Thr Leu Thr Glu Ala
            260                 265                 270

Arg Tyr Leu Leu Asp His Phe Leu Ser Met Gly Ile Asn Lys Gly Leu
        275                 280                 285

Gln Ala Ala Gln Lys Glu Ala Gln Ile Lys Val Leu Glu Gly Arg Leu
    290                 295                 300

Lys Gln Thr Glu Ile Thr Ser Ala Thr Gln Asn Gln Leu Leu Phe His
305                 310                 315                 320

Met Leu Lys Glu Lys Ala Glu Leu Asn Pro Glu Leu Asp Ala Leu Leu
                325                 330                 335

Gly His Ala Leu Gln Asp Leu Asp Ser Val Pro Leu Glu Asn Val Glu
            340                 345                 350

Asp Ser Thr Asp Glu Asp Ala Pro Leu Asn Ser Pro Gly Ser Glu Gly
        355                 360                 365

Ser Thr Leu Ser Ser Asp Leu Met Lys Leu Cys Gly Glu Val Lys Pro
    370                 375                 380

Lys Asn Lys Ala Arg Arg Arg Thr Thr Thr Gln Met Glu Leu Leu Tyr
385                 390                 395                 400

Ala Asp Ser Ser Glu Leu Ala Ser Asp Thr Ser Thr Gly Asp Ala Ser
                405                 410                 415

Leu Pro Gly Pro Leu Thr Pro Val Ala Glu Gly Gln Glu Ile Gly Met
            420                 425                 430

Asn Thr Glu Thr Ser Gly Thr Ser Ala Arg Glu Lys Glu Leu Ser Pro
        435                 440                 445

Pro Pro Gly Leu Pro Ser Lys Ile Gly Ser Ile Ser Arg Gln Ser Ser
    450                 455                 460

Leu Ser Glu Lys Lys Ile Pro Glu Pro Ser Pro Val Thr Arg Arg Lys
465                 470                 475                 480

Ala Tyr Glu Lys Ala Glu Lys Ser Lys Ala Lys Glu Gln Lys His Ser
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                485                 490                 495

Asp Ser Gly Thr Ser Glu Ala Ser Leu Ser Pro Pro Ser Ser Pro Pro
            500                 505                 510

Ser Arg Pro Arg Asn Glu Leu Asn Val Phe Asn Arg Leu Thr Val Ser
        515                 520                 525

Gln Gly Asn Thr Ser Val Gln Gln Asp Lys Ser Asp Glu Ser Asp Ser
    530                 535                 540

Ser Leu Ser Glu Val His Ser Arg Ser Ser Arg Arg Gly Ile Ile Asn
545                 550                 555                 560

Pro Phe Pro Ala Ser Lys Gly Ile Arg Ala Phe Pro Leu Gln Cys Ile
                565                 570                 575

His Ile Ala Glu Gly His Thr Lys Ala Val Leu Cys Val Asp Ser Thr
            580                 585                 590

Asp Asp Leu Leu Phe Thr Gly Ser Lys Asp Arg Thr Cys Lys Val Trp
        595                 600                 605

Asn Leu Val Thr Gly Gln Glu Ile Met Ser Leu Gly Gly His Pro Asn
    610                 615                 620

Asn Val Val Ser Val Lys Tyr Cys Asn Tyr Thr Ser Leu Val Phe Thr
625                 630                 635                 640

Val Ser Thr Ser Tyr Ile Lys Val Trp Asp Ile Arg Asp Ser Ala Lys
                645                 650                 655

Cys Ile Arg Thr Leu Thr Ser Ser Gly Gln Val Thr Leu Gly Asp Ala
            660                 665                 670

Cys Ser Ala Ser Thr Ser Arg Thr Val Ala Ile Pro Ser Gly Glu Asn
        675                 680                 685

Gln Ile Asn Gln Ile Ala Leu Asn Pro Thr Gly Thr Phe Leu Tyr Ala
    690                 695                 700

Ala Ser Gly Asn Ala Val Arg Met Trp Asp Leu Lys Arg Phe Gln Ser
705                 710                 715                 720

Thr Gly Lys Leu Thr Gly His Leu Gly Pro Val Met Cys Leu Thr Val
                725                 730                 735

Asp Gln Ile Ser Ser Gly Gln Asp Leu Ile Ile Thr Gly Ser Lys Asp
            740                 745                 750

His Tyr Ile Lys Met Phe Asp Val Thr Glu Gly Ala Leu Gly Thr Val
        755                 760                 765

Ser Pro Thr His Asn Phe Glu Pro Pro His Tyr Asp Gly Ile Glu Ala
    770                 775                 780
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Leu Thr Ile Gln Gly Asp Asn Leu Phe Ser Gly Ser Arg Asp Asn Gly
785                 790                 795                 800

Ile Lys Lys Trp Asp Leu Thr Gln Lys Asp Leu Leu Gln Gln Val Pro
                805                 810                 815

Asn Ala His Lys Asp Trp Val Cys Ala Leu Gly Val Val Pro Asp His
            820                 825                 830

Pro Val Leu Leu Ser Gly Cys Arg Gly Gly Ile Leu Lys Val Trp Asn
        835                 840                 845

Met Asp Thr Phe Met Pro Val Gly Glu Met Lys Gly His Asp Ser Pro
    850                 855                 860

Ile Asn Ala Ile Cys Val Asn Ser Thr His Ile Phe Thr Ala Ala Asp
865                 870                 875                 880

Asp Arg Thr Val Arg Ile Trp Lys Ala Arg Asn Leu Gln Asp Gly Gln
                885                 890                 895

Ile Ser Asp Thr Gly Asp Leu Gly Glu Asp Ile Ala Ser Asn
            900                 905                 910
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oigonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

TNCTCGGTTAT ATGGAGGACG AATAGACT 29

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CTCTTTATGA GCATGATATG GCTTCAG 27

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CNTGCTGCCCG ACTTAAACTG AGAACCAA 29

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GNGGACAACTC CCATAGTTGA GGTTTGTC 29

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TNGGAAGAGTG ACCCAGGGGC CCAAAGCA 29

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

CNCTGCAAGCG AGTGGTTTTC AGGGCTGT 29

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

TNGAGCCAAGG AGAGAGCAGA CAGGCTGA 29

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

ANCCCCCAGAA GTACAAGGAC ATGCCAAG 29

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

CNATAGCATCA GCATCAACAT GGTGACAA 29

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CTCCATTCTC CTTGACTATC TTCTCCC 27

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

TNCCTGGTGCC ATCATGATTG TATGAGGC 29

What is claimed is:

1. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 22 to nucleotide 462;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ1_1 deposited under accession number ATCC 98278;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ1_1 deposited under accession number ATCC 98278;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ1_1 deposited under accession number ATCC 98278;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ1_1 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

2. A composition of claim 1 wherein said polynucleotide is operably linked to at least one expression control sequence.

3. A host cell transformed with a composition of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.

5. A process for producing a protein encoded by a composition of claim 2, which process comprises:

(a) growing a culture of the host cell of claim 3 in a suitable culture medium; and

(b) purifying said protein from the culture.

6. A protein produced according to the process of claim 5.

7. The protein of claim 6 comprising a mature protein.

8. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 52 to amino acid 147;

(c) fragments of the amino acid sequence of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone AJ1_1 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins.

9. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.

10. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 52 to amino acid 147.

11. The composition of claim 8, further comprising a pharmaceutically acceptable carrier.

12. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 11.

13. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:1 or SEQ ID NO:3.

14. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:4;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:4 from nucleotide 7 to nucleotide 1647;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:4 from nucleotide 1 to nucleotide 305;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AQ73_3 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AQ73_3 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AQ73_3 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AQ73_3 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:5;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:5 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

15. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:5;

(b) the amino acid sequence of SEQ ID NO:5 from amino acid 1 to amino acid 68;

(c) fragments of the amino acid sequence of SEQ ID NO:5; and

(d) the amino acid sequence encoded by the cDNA insert of clone AQ73_3 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins.

16. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:4.

17. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6 from nucleotide 62 to nucleotide 757;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6 from nucleotide 357 to nucleotide 703;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BG142_1 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BG142_1 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG142_1 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG142_1 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:7;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:7 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

18. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:7;

(b) the amino acid sequence of SEQ ID NO:7 from amino acid 184 to amino acid 214;

(c) fragments of the amino acid sequence of SEQ ID NO:7; and

(d) the amino acid sequence encoded by the cDNA insert of clone BG142_1 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins.

19. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:6.

20. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8 from nucleotide 404 to nucleotide 535;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8 from nucleotide 1 to nucleotide 666;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BV66_1 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BV66_1 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BV66_1 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BV66_1 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:9;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:9 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

21. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:9;

(b) the amino acid sequence of SEQ ID NO:9 from amino acid 1 to amino acid 38;

(c) fragments of the amino acid sequence of SEQ ID NO:9; and

(d) the amino acid sequence encoded by the cDNA insert of clone BV66_1 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins.

22. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:8.

23. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:10;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:10 from nucleotide 1204 to nucleotide 1389;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:10 from nucleotide 881 to nucleotide 1380;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BV291_3 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BV291_3 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BV291_3 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BV291_3 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:11;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:11 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

24. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:11;

(b) the amino acid sequence of SEQ ID NO:11 from amino acid 1 to amino acid 59;

(c) fragments of the amino acid sequence of SEQ ID NO:11; and

(d) the amino acid sequence encoded by the cDNA insert of clone BV291_3 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins.

25. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:10.

26. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 189 to nucleotide 1115;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 1 to nucleotide 451;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CK201_1 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CK201_1 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CK201_1 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CK201_1 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:13 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

27. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:13;

(b) the amino acid sequence of SEQ ID NO:13 from amino acid 1 to amino acid 88;

(c) fragments of the amino acid sequence of SEQ ID NO:13; and

(d) the amino acid sequence encoded by the cDNA insert of clone CK201_1 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins.

28. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:12.

29. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14 from nucleotide 117 to nucleotide 923;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14 from nucleotide 174 to nucleotide 923;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14 from nucleotide 1 to nucleotide 316;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CQ331_2 deposited under accession number ATCC 98278;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CQ331_2 deposited under accession number ATCC 98278;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CQ331_2 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CQ331_2 deposited under accession number ATCC 98278;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:15;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:15 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

30. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:15;

(b) the amino acid sequence of SEQ ID NO:15 from amino acid 1 to amino acid 57;

(c) fragments of the amino acid sequence of SEQ ID NO:15; and

(d) the amino acid sequence encoded by the cDNA insert of clone CQ331_2 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins.

31. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:14.

32. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16 from nucleotide 223 to nucleotide 483;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16 from nucleotide 22 to nucleotide 397;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CT550_1 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CT550_1 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CT550_1 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CT550_1 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:17;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:17 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

33. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:17;

(b) the amino acid sequence of SEQ ID NO:17 from amino acid 1 to amino acid 58;

(c) fragments of the amino acid sequence of SEQ ID NO:17; and

(d) the amino acid sequence encoded by the cDNA insert of clone CT550_1 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins.

34. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:16.

35. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 112 to nucleotide 969;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 154 to nucleotide 969;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 1 to nucleotide 423;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CT585_1 deposited under accession number ATCC 98278;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CT585_1 deposited under accession number ATCC 98278;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CT585_1 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CT585_1 deposited under accession number ATCC 98278;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:19;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

36. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:19;

(b) the amino acid sequence of SEQ ID NO:19 from amino acid 1 to amino acid 104;

(c) fragments of the amino acid sequence of SEQ ID NO:19; and

(d) the amino acid sequence encoded by the cDNA insert of clone CT585_1 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins.

37. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:18.

38. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20 from nucleotide 37 to nucleotide 2766;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20 from nucleotide 243 to nucleotide 789;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CT797_3 deposited under accession number ATCC 98278;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CT797_3 deposited under accession number ATCC 98278;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CT797_3 deposited under accession number ATCC 98278;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CT797_3 deposited under accession number ATCC 98278;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:21;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:21 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

39. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:21;

(b) the amino acid sequence of SEQ ID NO:21 from amino acid 75 to amino acid 251;

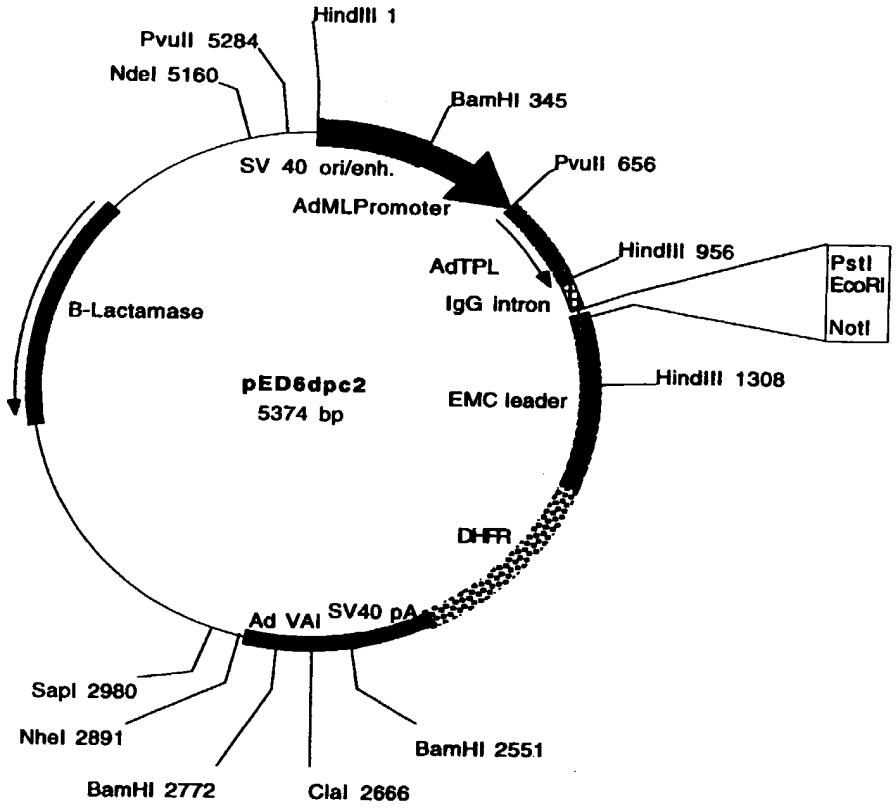
(c) fragments of the amino acid sequence of SEQ ID NO:21; and

(d) the amino acid sequence encoded by the cDNA insert of clone CT797_3 deposited under accession number ATCC 98278;

the protein being substantially free from other mammalian proteins.

40. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:20.

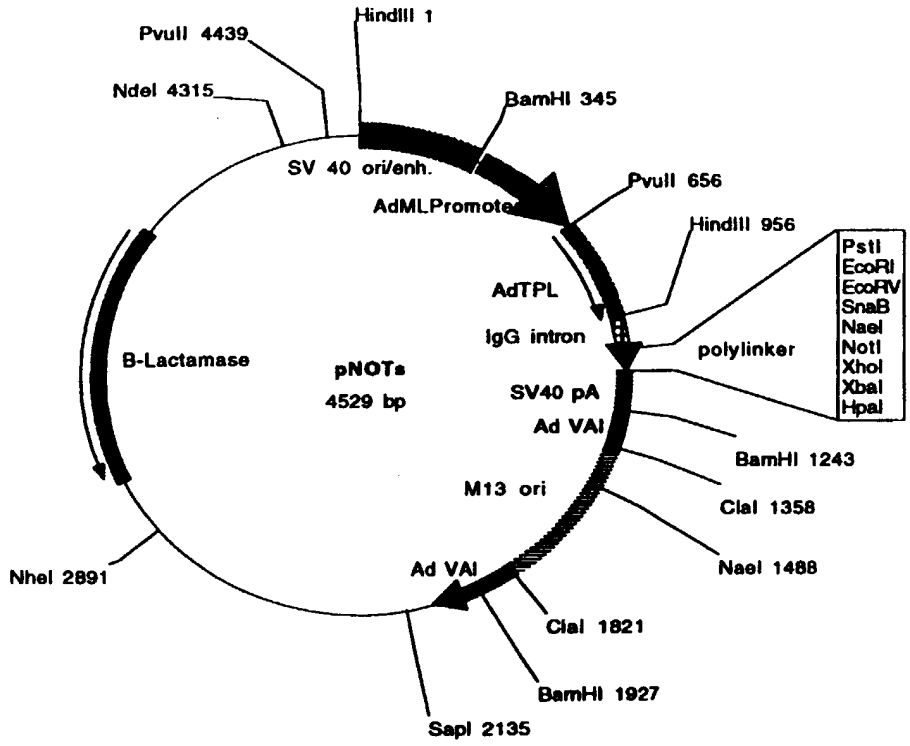
FIGURE 1A



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

FIGURE 1B



Plasmid name: pNOTs
Plasmid size: 4529 bp

Comments/References: pNOTs is a derivative of pMT2 (Kaufman et al,1989. Mol.Cell.Biol.9:1741-1750). DHFR was deleted and a new polylinker was inserted between EcoRI and HpaI. M13 origin of replication was inserted in the ClaI site. SST cDNAs are cloned between EcoRI and NotI